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PhenoFluorMix: Practical Chemoselective Deoxyfluorination of Phenols

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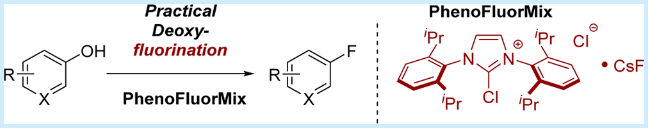
Supporting Information

ABSTRACT: A practical deoxyfluorination with novel deoxyfluorinating reagent PhenoFluorMix, a mixture of N,N'-1,3-bis(2,6-diisopropylphenyl)chloroimidazolium chloride and CsF, is presented. PhenoFluorMix overcomes the challenges associated with hydrolysis of PhenoFluor. PhenoFluorMix does not hydrolyze, is readily available on decagram scale, and is storable in air. In this paper, we demonstrate the practicality of the reagent and exhibit the deoxyfluorination of a variety of phenols and heterocycles.



PhenoFluor is a commercially available, useful deoxyfluorinating reagent applicable to deoxyfluorination of a variety of phenols and aliphatic alcohols.[1,2] Especially in the pharmaceutical and agrochemical industries, PhenoFluor can be employed for rapid analogue synthesis. However, PhenoFluor is moisture sensitive.[1d] Because PhenoFluor readily hydrolyzes, it needs to be stored over the long term in a protective atmosphere, such as in an N_2-filled glovebox, which reduces the practical utility of the reagent. Herein, we report the novel deoxyfluorinating reagent PhenoFluorMix, which overcomes the challenges associated with hydrolysis of PhenoFluor; in contrast to PhenoFluor, PhenoFluorMix does not hydrolyze and can be dried prior to deoxyfluorination (Figure 1). Conceptually, deoxyfluorination with PhenoFluorMix is of fundamental interest by virtue of fluorination being observed exclusively despite the presence of two equivalents of chloride. A chemoselective halogenation reaction that proceeds with fluoride but not with the other halides is uncommon; in fact, fluorination is virtually always more difficult to achieve than other halogenation reactions.[3]

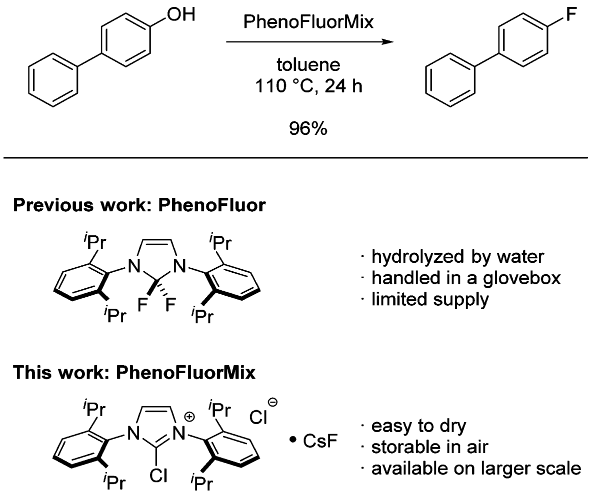


Figure 1. Comparison of PhenoFluor with PhenoFluorMix.

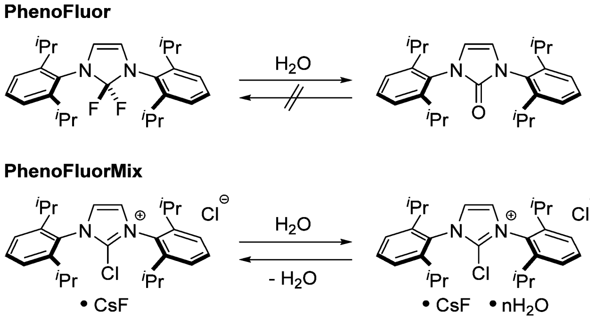
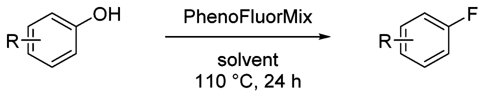


Figure 2. Effect of water on PhenoFluor and PhenoFluorMix.

Table 1. Solvent Effect on Deoxyfluorination of Phenols[a]



solvent	R = *p*-Ph (%)	R = *p*-OMe (%)	R = *o*-OMe (%)
DME	91 (100 °C)	53 (100 °C)	
dioxane	94	43	12
diglyme		78	12
toluene	96	34	14
o-xylene	94	87	66 (140 °C)
anisole	97	91	27 (140 °C)

[a] Yields were determined by ^{19}F NMR with 1-fluoro-3-nitrobenzene as an internal standard.

Over the past five years, a variety of transition-metal-catalyzed or -mediated fluorination reactions have been developed.[4−7] Many of them exhibit improvements with

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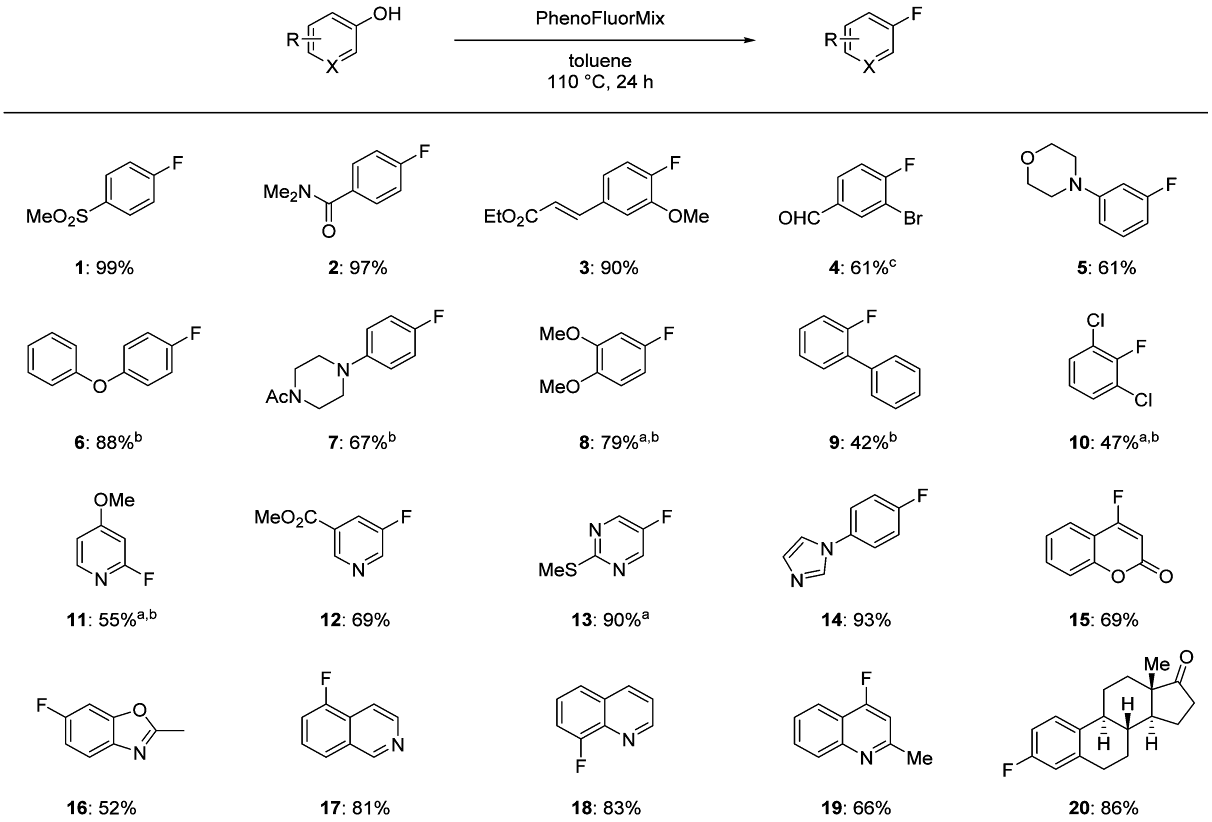
Scheme 1. Deoxyfluorination with PhenoFluorMix



[a]Products were volatile; yields were determined by ^{19}F NMR with 1-fluoro-3-nitrobenzene as an internal standard. [b]Reactions were performed in xylene at 140 °C. [c]Reaction time was 20 min: prolonged reaction time caused the decomposition of product.

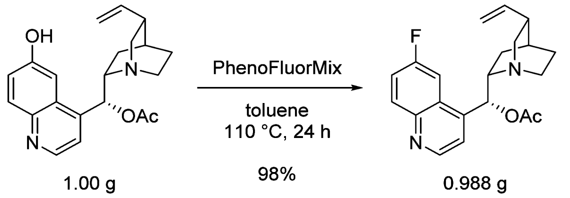
respect to reaction conditions compared to conventional reactions such as the Balz–Schiemann reaction. However, with respect to practicality, we feel that fluorination reactions require further development. For example, Ag-catalyzed fluorination reported by our group requires the synthesis and use of toxic aryl stannanes.[5a] Buchwald's Pd-catalyzed fluorination has a broad substrate scope including heterocycles, but electron-rich substrates lacking an *ortho* substituent can afford constitutional isomers.[4f,s] Cu-mediated or -catalyzed fluorinations of aryl iodides,[6b] boronates,[6c] trifluoroborates,[6d,g] and iodonium salts[6f] have been reported, but basic nitrogen-containing heterocycles are challenging substrates for such methods. Furthermore, reduced products generated by protodehalogenations or protodemetalations can be a substantial challenge for several transition-metal-based fluorination reactions because these products are difficult to separate during purification.[8]

PhenoFluorMix is a 1:2 (by weight) mixture of *N*,*N*′-1,3-bis(2,6-diisopropylphenyl)chloroimidazolium chloride[9,1d] and CsF. In contrast to PhenoFluor, PhenoFluorMix, even when wet or treated with water, does not hydrolyze to the urea (Figure 2). Because of its stability toward moisture, PhenoFluorMix is easily prepared on decagram scale on the bench (also commercially available from Sigma-Aldrich, cat. no. 797537). Furthermore, unlike PhenoFluor, PhenoFluorMix is storable under ambient atmosphere for at least 4 months without any detectable decomposition. While the deoxyfluorination with PhenoFluorMix still should be conducted under anhydrous reaction conditions, PhenoFluorMix can be dried prior to reaction, even if it adsorbs water during storage. We obtained optimal yields of deoxyfluorination with PhenoFluorMix when the reagent was heated at 140 °C for 1 h under vacuum immediately prior to use.

Deoxyfluorination of 4-hydroxybiphenyl with PhenoFluorMix proceeds efficiently in several solvents including polar solvents such as acetonitrile, DMF, and DMSO (see the Supporting Information). However, we found that only ethers and aromatic solvents worked well for electron-rich substrates such as 4-methoxyphenol (Table 1). For substrates that are both electron rich and sterically hindered, such as 2-methoxyphenol, heating at 140 °C in xylene proved to be most effective. Consequently, heating at 110 °C in dioxane or toluene is a suitable reaction condition for most substrates, whereas heating at 140 °C in xylene is effective for electron-rich and sterically hindered substrates.

As shown in Scheme 1, a variety of phenols, including both electron-deficient and electron-rich aromatics, as well as heterocycles, are deoxyfluorinated with PhenoFluorMix. Electron-rich phenols, such as *p*-alkoxy or *p*-alkylamino phenols, the corresponding fluorides of which are often seen in pharmaceuticals (**6**–**8**),[10] and sterically hindered phenols (**9**, **10**) underwent deoxyfluorination. Basic nitrogen-containing heterocycles, such as pyridines (**11**, **12**), imidazole (**14**), isoquinoline (**17**), and quinolines (**18**, **19**), are well tolerated, so are aldehydes and ketones (**4**, **20**), olefins (**3**), sulfides (**13**), and halogens (**4**, **10**). Deoxyfluorination with PhenoFluorMix can be scaled up to gram scale (eq 1). Throughout our study, fluorine constitutional isomers or reduced products were not observed, which simplified purification. However, removal of the resulting urea is inevitable. We also found that, as with

PhenoFluor,[1a] deoxyfluorination of phenols bearing a primary or secondary carboxamide or carbamate is challenging. In addition, five-membered heterocycles are generally unsuitable substrates for the deoxyfluorination with PhenoFluorMix.



(1)

The deoxyfluorination with PhenoFluorMix may not proceed via in situ formation of PhenoFluor but via uronium intermediates.[1a] We have obtained no evidence for the formation of PhenoFluor and therefore believe that deoxyfluorination with PhenoFluorMix is not an in situ version of our previously published PhenoFluor reaction. In view of the fact that electron-rich phenols underwent deoxyfluorination, the fluorination is likely not a simple S_NAr reaction.[11] Moreover, the formation of aryl chlorides was not observed in the reactions with PhenoFluorMix. Even in the presence of 10 equiv of CsCl, no chlorinated product was detected. Conceptually, this chemoselectivity—deoxyfluorination versus other deoxyhalogenation provides a fundamentally new opportunity for C−F bond formation. While the origin of the unusual selectivity is not yet apparent, PhenoFluorMix provides a promising mechanistic entry to chemoselective fluorination chemistry that other conventional and modern fluorination reactions lack.

In conclusion, we have developed a practical phenol deoxyfluorination with PhenoFluorMix. The novel reagent does not easily hydrolyze, is readily available on decagram scale, and is storable in air. The reaction can be performed on the bench, does not require separation of fluorine constitutional isomers or reduced product, and shows broad substrate scope and high functional group tolerance. We believe PhenoFluorMix will provide facile access to practical late-stage deoxyfluorination of small molecules and, currently, constitutes one of the most general and practical reactions for late-stage fluorination up to gram scale. Mechanistically, it could lead to a better understanding of chemoselective fluorination chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectroscopic characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): T.R. may financially benefit from PhenoFluorMix sales.

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